UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: EPHEDRA PRODUCTS LIABILITY LITIGATION	:	04 M.D. 1598 (JSR)
PERTAINS TO ALL CASES	:	

FOURTH AMENDED GENERIC EXPERT REPORT OF STEVEN R. LEVINE, M.D.

(Content edited to conform to the directives of the Court and Special Master)

Fed. R. Civ. Proc. 26

I. INTRODUCTION

A. Background and Qualifications

1. I am a medical doctor with a specialization in neurology and a subspecialization in cerebrovascular diseases and stroke by way of a two-year fellowship post residency. I am a full time faculty and tenured professor at the Mount Sinai School of Medicine and Medical Center in New York City. I have committed my full-time profession to the diagnosis, care, prevention, and treatment of stroke. I am part of an active stroke program there, and I am Director of Cerebrovascular Education. My research has been funded by the NIH (continuously since 1990) and the American Heart Association, and I serve on the editorial board of several peer-reviewed journals, including *Stroke* and *Clinical Neuropharmacology*. I am the editor for the National Stroke Association's Stroke-Clinical Updates and MEDLINK. I am a board certified neurologist (as of November 1986).

2. One of my particular research interests is the ability of drugs to cause or contribute to stroke. I have published approximately 10 articles in the peer reviewed medical literature about sympathomimetic drug-induced strokes in the young, many dealing with cocaine, as well as other sympathomimetics and diet (anorectic) agents. I wrote more than a decade ago

in the journal *Stroke*, Vol. 21, No. 6, June 1990 that "Other sympathomimetic agents, especially phenylpropanolamine, ephedrine, and amphetamine, have also been associated with multiple bilateral intracranial hemorrhages." (p. 962). A copy of my curriculum vitae and complete bibliography is attached.

3. I have reviewed many articles within the published medical literature on ephedra and its main active ingredient, ephedrine, as well as reports summarizing data to and from the FDA concerning adverse events associated with ephedra products. I have also reviewed published literature on the physiological, pharmacological, and toxic effects of ephedra products and ephedrine. In addition, I have reviewed the additional scientific literature on other sympathomimetic agents, including PPA, which share similar pharmacological structures and side effect profiles. I have also reviewed several expert reports concerning sympathomimetics.

4. I have treated stroke patients where I believed that sympathomimetics caused or contributed to the etiology.

5. Based on my experience, review of the literature, pharmacokinetics, known sympathomimetic and cardiovascular stimulant effects of ephedra and ephedrine, including prior reports and studies of associated cerebrovascular disease, I believe that ephedra may likely be a contributing cause of ischemic and hemorrhagic stroke in some people.

B. Summary of Opinions

6. Hemorrhagic stroke is defined as an injury to the brain, secondary either to bleeding within the brain itself (intracerebral hemorrhage, or "ICH") or to bleeding within the cerebrospinal fluid-filled space surrounding the brain (subarachnoid hemorrhage or "SAH"). Hemorrhagic stroke is a relatively uncommon disease, especially in young populations (children and adults under 50 years of age).

7. Ischemic stroke is generally defined by an injury to the brain, secondary to an occlusion of a blood vessel, which deprives adequate blood flow to parts of the brain. The occlusion is most often due to a blood clot that originated in the brain ("thrombosis") or a clot that originated elsewhere in the body and traveled to the brain to obstruct an intracranial blood

vessel ("embolus"). However, stroke may also be caused by underlying vascular diseases or conditions such as vasculitis, dissection, or an acute elevation of blood pressure. While there are several risk factors for ischemic stroke, sympathomimetic drug use and abuse is a common risk factor in young, otherwise healthy populations.

8. Strokes of either subtype may be fatal. Stroke may also result in serious and permanent disability, including brain damage, paralysis (weakness), aphasia, visual loss, memory loss, coordination and speech problems, and neurocognitive impairment.

9. Ephedra refers to a plant genus, also referred to in Chinese as "ma-huang." Ephedra is a botanical (plant) source of ephedrine alkaloids and is made and sold over-the-counter as a "natural" stimulant. The popularity of ephedra soared during the 1990s because of its stimulant effects. [Gurley, Dec. 1998].

10. Ephedrine is a potent vasoconstrictor and was an active ingredient in many over-the-counter "herbal" ephedra supplements used as energy enhancers and appetite suppressants. Ephedrine is a sympathomimetic or stimulant agent with alpha-adrenergic and beta-adrendergic activity. Ephedrine possesses a greater degree of toxicity than the newer beta-adrenergic agonists. The therapeutic index for ephedrine is low. Thus, even a small increase in the dose of ephedrine may result in a greatly magnified toxic response. Ephedra alkaloids also contain small amounts of pseudoephedrine, a somewhat weaker sympathomimetic agent. In the body, a variable percentage of ephedra breaks down into phenylpropanolamine ("PPA"). PPA is also an amphetamine-like sympathomimetic and may cause hemorrhagic and ischemic stroke.

11. Ephedra dietary supplements often contained caffeine, which enhances the stimulant effects of sympathomimetic drugs, including ephedrine. [Glennon and Young 2000; Haller, June 2002] When ingested in lower dosages, ephedra alkaloids may cause vasoconstriction, spikes in blood pressure, rapid or irregular heartbeats, nervousness, headache, seizures and insomnia. In some people, especially those who have underlying vascular diseases or abnormalities or who are otherwise susceptible, ephedra supplements may likely be a contributing cause of severe adverse reactions, including stroke, cardiac disturbances, and even

death. However, even in some otherwise healthy young people, ephedra may likely be a contributing cause of stroke.

12. There has been extensive published literature documenting the adverse reactions to ephedra and its active ingredient, ephedrine. These include detailed review articles (including in the *NEJM*), case reports and case series, toxicological studies, animal studies, human controlled clinical studies of blood pressure elevation and cardiac arrhythmias, as well as textbooks and other learned treatises and published professional medical guidelines.

13. Moreover, ephedrine shares the characteristics of other amphetamine-like sympathomimetic drugs that also have been associated in the medical literature with both hemorrhagic and ischemic strokes. Based on these multiple, consistent, and persuasive lines of evidence, it is my opinion that ephedra supplements, which contain ephedrine and often caffeine, may likely be a contributing cause of stroke in some people.

II. OVERVIEW OF EPHEDRINE, THE ACTIVE INGREDIENT IN EPHEDRA SUPPLEMENTS

14. Ephedra, or the Chinese herb *ma huang* is derived from dried, above-the-ground parts of the plant known as ephedra sinica. Ephedra is a natural source of ephedrine alkaloids, such as ephedrine, psueoephedrine, norephedrine (PPA), methylephedrine, norpseudoephedrine, and methylpseudophedrine.

15. Ephedrine is the principal active ingredient in ephedra "herbal" dietary supplements. Ephedrine is a sympathomimetic (stimulant) agent with both alpha-adrenergic and beta-adrenergic activity, meaning it is capable of stimulating the sympathetic nervous system (part of the body's autonomic nervous system, which controls heart rate, blood pressure, vascular tone and other cardiovascular functions). Ephedrine resembles amphetamine in action and in structure (see figure below).

16. Ephedrine is present both in herbal products (e.g., ma huang) and in pure form in bronchodilators, cold remedies and nasal decongestants. Before the FDA ordered the withdrawal of ephedrine containing dietary supplements from the market, doses ranging from 10

to 50 mg of ephedrine were found in over-the-counter products, as well as some prescription formulations. However, the recommended *daily* dose of ephedrine in ephedra dietary supplements may be much higher and varies widely from one product to another. [Haller and Benowitz 2000; Gurley 2000]

17. Ephedrine is a stereoisomer of pseudoephedrine, a widely used decongestant. Botanical ephedrine (found in ephedra supplements) often contains not only ephedrine, but pseudoephedrine, norephedrine, and sometimes methylephedrine. Norephedrine is structurally identical to PPA. However, the enantiomer of PPA found in herbal ephedra is (-)-norephedrine, which is more potent than the isomer present in PPA over-the-counter products. [Gurley 2000] As sympathomimetics, all of these drugs work similarly to amphetamines by directly activating the alpha-adrenergic receptors of the sympathetic nervous system and by releasing endogenous catecholamines. In other words, all of these drugs are vasoconstrictors and affect the same types of cell receptors within the central nervous and vascular systems. The main cardiovascular effect is constriction of arteries and veins. To a lesser extent, ephedrine has beta-adrenergic stimulation, which produces increased heart rate and increased force of heart contraction. Because of its vasoconstriction and blood pressure elevating properties, ephedrine was at one time widely used to treat shock (low blood pressure) or to prevent a fall in blood pressure. Ephedrine is reported to be three-to four times as potent in its cardiovascular activity than pseudoephedrine. [Drew 1978.]

18. Ephedrine is primarily eliminated from the body by excretion of unchanged drug by the kidney. A small percentage is metabolized in the liver, primarily to norephedrine (PPA). Renal clearance is higher in acid urine than in alkaline urine. In acid urine, 80 to 90% of a dose is excreted in the urine in 24 hours, whereas in alkaline urine, 20 to 35% is excreted within the same timeframe. Thus, individuals whose urine is alkaline will generally retain ephedrine alkaloids in their systems longer than individuals with acidic urine. [Haller 2002.]

19. Most ephedra dietary supplements also contain various forms of caffeine. For example, the supplement Metabolift also contained 100 mg of caffeine from guarana seed extract [Haller 2002]. A clinical study conducted by Haller *et al.* demonstrates that caffeine may potentiate the stimulant effects of ephedrine alkaloids in dietary supplements. At moderate doses, caffeine increases blood pressure, slightly decreases heart rate, releases catecholamines and renin. Haller and colleagues confirmed that caffeine combined with ephedrine – which also increases catecholamine release and cardiac contractility, heart rate and blood pressure – may likely be a contributing cause of significant pharmacological responses in humans. [Haller 2002.] The Haller study was consistent with findings in animal models. [Young R 1998.]

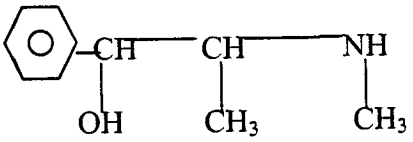
20. Several studies have shown that caffeine and PPA have an additive effect on blood pressure. [Brown 1991; Lake 1990]. In 1983, the FDA banned the marketing of all existing non-herbal over-the-counter dietary products that contained both phenylpropanolamine (PPA) and caffeine because the combination could cause dangerous central nervous system side effects. The FDA also banned OTC combinations of ephedrine and caffeine. [48 FR 52513 (Nov. 18, 1983); 47 F.R. 35344 (Aug. 13, 1982)]. Taken together, studies on sympathomimetics and caffeine suggest that herbal supplements containing ephedra and caffeine are "natural" equivalents to the amphetamine look-alike drugs banned by the FDA over 20 years ago. [Gurley 2000] Given that many Americans use caffeine in multiple forms (coffee, tea, soda, e.g.), they may be at increased exposure to risk of the adverse effects of PPA and ephedrine.

21. The relevance of PPA to ephedrine is important. Notably, PPA is structurally similar to ephedrine and shares similar pharmacological properties. [Lake and Quirk 1984] The more potent isomer of PPA is also a metabolite of ephedrine. That is, the body breaks down ephedrine into varying percentages of norephedrine (PPA) before it is excreted. In 2000, the FDA asked drug manufacturers to discontinue marketing over-the-counter appetite suppressants and nasal decongestants containing PPA because of its association with hemorrhagic strokes. Subsequently, the FDA took ephedrine off the market because of its role in adverse cardiovascular events, including stroke.

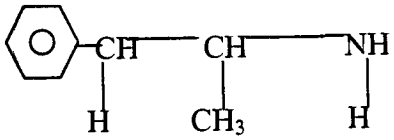
III. AS A SYMPATHOMIMETIC AMINE, EPHEDRINE IS A POWERFUL VASOCONSTRICTOR AND IS SIMILAR TO AMPHETAMINE AND PHENYLPROPANOLAMINE, BOTH IN STRUCTURE AND FUNCTION

A. Similar Chemical Structures of Selected Sympathomimetics

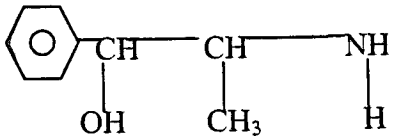
22. Sympathomimetics are a class of drugs that stimulate the central nervous system and have direct effects on blood vessels. This can lead to alterations in blood tone and diameter, including vasospasm, increased blood pressure – sometimes extremely high – and changes in neurotransmitters (chemicals that are secreted so that one cell can "talk" to another cell) that can alter the brain and blood vessel function.



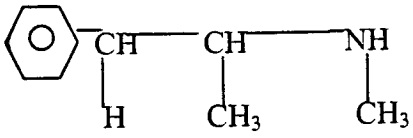
Ephedrine



Amphetamine



Phenylpropanolamine (PPA)



Methamphetamine

 = Benzene ring (C_6H_6)

23. It is a well recognized medical principle that if one sympathomimetic drug may likely be a contributing cause of an adverse effect on human vasculature, it is reasonable to infer that other sympathomimetic drugs may likely be a contributing cause of the same adverse

effect. [Case, Ch. 25, *Stroke* 3d Ed. 1998 pp. 659-661] In the textbook *Primer on Cerebrovascular Disease,* Dr. Michael Sloan observed, "For amphetamine and sympathomimetic agents, structure-activity relationships explain why certain compounds are likely to produce clinically important central nervous system effects." [Sloan, Ch. 113 1997]

24. The mechanism by which ephedrine and other decongestants produce their biological action is generally through activation of selected receptors found on very small blood vessels of the nasal mucosa. Activation of these receptors by either direct binding of the sympathomimetic agents to the binding site of the receptor, or by enhanced release of norepinephrine, produces vasoconstriction (narrowing of the blood vessels). The vasoconstriction decreases blood flow through the nasal mucosa and results in shrinking of the mucosa tissue. Oral decongestants can also affect the cardiovascular, urinary, central nervous, and endocrine systems. When ephedrine and other alpha-adrenergic agonists are taken systemically in doses sufficient to constrict blood vessels in the nasal mucosa, they may also have the same effect on blood vessels in other parts of the body as well. All of these drugs may likely be a contributing cause of vasoconstriction, or narrowing of blood vessels, and increase heart rate and blood pressure.

25. Ephedrine and other sympathomimetics have clear-cut effects on neurotransmitters and physiological actions. Effects on neurotransmitters take place at the central nervous system (CNS) terminals as summarized in the tables below. The first table summarizes the effects of sympathomimetics on catecholamines. The second table summarizes the effects on serotonin and dopamine.

Tables 1 and 2:

	Catecholamines			
Drug	**↓ Re-Uptake**	**↑ Release**	**↓ Brain levels**	**↑ Plasma levels**
Amphetamines	-	+	-	-
OTC sympathomimetics (incl. Ephedrine)	-	+	-	-
Cocaine	+	-	-	+

	Serotonin		Dopamine	
Drug	**↓ Re-Uptake**	**↑ Release**	**↓ Re-Uptake**	**↑ Release**
Amphetamines	-	+	-	+
OTC sympathomimetics (incl. Ephedrine)	-	-	-	-
Cocaine	+	-	-	-

(legend: OTC = over the counter; + = presence of effect; - = absence of effect)
(note: other drugs associated with stroke have similar effects but are not detailed in these tables) Tables adapted from Sloan et al 1998.

26. Sympathomimetics, including ephedrine, gain entry into the CNS and have a variety of effects on neurotransmitters. Many drugs, including ephedrine, release catecholamines from central noradrenergic nerve terminals. Catecholamines are chemicals that the body uses as messengers to stimulate certain structures. Sometimes, similar effects on central serotonergic and dopaminergic neurotransmission are observed. These effects may produce mild to profound blood pressure elevation, at times with increased or decreased heart rate. Peripheral and central/cerebral vasoconstriction may occur. The pathophysiologic effects of relevant drugs are summarized in the following table.

Table 3:

Drug	**Vasoconstriction**	**Hypertension**	**Arrhythmias**	**Hemostatic**
Amphetamines	+	+	+	-
OTC sympathomim. (incl. Ephedrine)	+	+	+	-
Cocaine	+	+	+	+

(legend: OTC = over the counter; + = presence of effect; - = absence of effect)
(note: other drugs associated with stroke have similar effects but are not detailed in these tables) Tables adapted from Sloan et al 1998.

27. Many drugs have vascular effects both on the peripheral and cerebral vessels, as shown in the table below. Vasospasm may be produced by cocaine and sympathomimetics, including ephedrine.

Table 4:

Drug	Vasospasm	Vasculopathy	Microaneurysm	Arteritis
Amphetamines	-	+	+	+
Ephedrine	+	-	-	+
Cocaine	+	+	+	+

Table adapted from Sloan et al 1998.

28. Sympathomimetics may have multiple effects on the cerebral vasculature and may be associated with inflammation in the cerebral vessels, constriction of the cerebral vessels, development of microaneurysms, and non-inflammatory alterations of the vessel wall. Similar effects have been seen in the myocardial (heart) vessels. All of these drugs may likely be a contributing cause of myocardial infarction as well. [Haller and Benowitz 2000] The vasoconstriction may be rapid, transient, or prolonged. Venule (small vein) vasospasm and postcapillary microhemorrhages have followed cocaine administration. Magnesium has been shown to produce a dose-dependent inhibition of cocaine-induced vasospasm. Magnesium is a natural calcium antagonist, and cocaine vasospasm is calcium dependent. [Sloan Ch. 114, 1998]

29. Experimentally, in rabbits subjected to angiography, low doses of cocaine or methamphetamine alone caused mild vasodilation. High doses of cocaine or methamphetamine alone led to mild basilar artery vasospasm. Co-administration of high doses of cocaine and methamphetamine led to severe basilar artery vasospasm. [Wang 1990]

30. In cats, topical application of cocaine in concentrations of 10^{-6} mol/L and 10^{-5} mo/L led to pial (superficial) arteriolar dilation, whereas a concentration of 10^{-4} led to dilation of all arterioles. This appeared to be beta-adrenergically mediated as the effects were blocked by propanolol. [Dohi 1990]

31. Experimental studies in monkeys suggest that norepinephrine (a sympathomimetic agent) instilled in the cerebrospinal fluid may likely be a contributing cause of biphasic vasospasm that is morphologically similar to the vasospasm seen after subarachnoid hemorrhage. In the rhesus monkey, methamphetamine injected intravenously produces an immediate (10-minute) decrease in vessel caliber in some animals, while other animals have

SAH with generalized vasospasm, multiple infarctions, edema, and small, petechial hemorrhages. [Rumbaugh 1971]

32. In monkeys and rats, exposure to methamphetamines and Ritalin (methylphenidate) for periods ranging from one week to one year produced occlusions of vessels, poor vascular filling, thrombosis, attenuated and fragmented brain arterioles and capillaries, dilated veinules, and microhemorrhages. [Rumbaugh et al. 1976]

33. A study of 71 rats given a combination of PPA and caffeine found that a single dose led to acute hypertension in both normotensive and hypertensive animals. Moreover, repeated doses produced cerebral hemorrhage in spontaneously hypertensive and stroke-prone rats. [Mueller 1984]

34. Concerning small, medium and large sized intracranial arteries, segmental narrowing or "beading" of vessels has been reported with amphetamines, phentermine, ephedrine, pseutoephedrine, and PPA. Various amphetamines and cocaine may likely be a contributing cause of large vessel stenosis or occlusion or small branch occlusion. These may take place extracranially or intracranially. Angiographic data in humans suggest that cocaine-associated stroke may be associated with normal appearing intracranial arteries or unusual disruption of the vessels' internal plastic lamina (as a potential pathologic correlate of vasospasm). [Green 1990, Konzen 1995]

35. Table 5 below summarizes the likely mechanisms of ischemic cerebrovascular disease associated with drug use/abuse specifically for sympathomimetics, including ephedrine. Mechanisms of hemorrhagic stroke are listed in Table 6.

Table 5: Ischemic Cerebrovascular Disease

Mechanisms	Amphetamines	OTC Sympathomimetics/Ephedrine	Cocaine
Arterial vasoconstriction			
Vasospasm	+	+	+
Vasculopathy	+	-	+
Arteritis	+	+	±
Foreign body embolism	+	-	-
Structural heart disease			
Arrhythmias	+	+	+
Cardiomyopathy	+	+	+
Myocardial infarction	+	+	+
Endocarditis	+	-	+
Small vessel disease/occl.	-	+	+
Prothrombotic tendency	-	-	+

Legend: OTC = over the counter, + = known association, - = no known association, ± = controversial. Table adapted from Sloan et al 1998.

Table 6: Hemorrhagic Cerebrovascular Disease

Mechanisms	Amphetamines	OTC Sympathomimetics/Ephedrine	Cocaine
Hypertension	+	+	+
Unmasking Pre-existing lesions			
Aneurysm	-	+	+
Arteriovenous malformation	+	+	+
Tumor	-	-	+
Lesion induction			
Microaneurysms	+	-	+
Arterioles	+	-	+
Venules	+	-	+
Arteritis/vasculopathy	+	+	+
Immune perturbations	+	+	-
Drug interactions			
MAO inhibitors	+	+	-
NSAIDS	-	+	-
OTC sympathomimetics	-	+	-
Ethanol	+	-	+
Reperfusion	±	±	+
Combination	+	+	+

Legend: OTC = over the counter, + = known association, - = no known association; ± = postulated, MAO = monoamine oxidase; NSAIDS = non-steroidal anti-inflammatory drugs. Table adapted from Sloan et al 1998.

B. Ephedrine, Like Other Sympathomimetics, Has a Low Therapeutic Index

36. The therapeutic window for a medication or drug is the range of blood levels that produce the desired pharmacologic effect without producing adverse effects. Drugs with wide or large therapeutic windows tend to be safer than drugs with narrow or small

therapeutic windows. The narrower the window, the more difficult it can be to dose a medication to maintain a therapeutic effect without adverse reactions. Ephedrine has a narrow therapeutic margin, similar to other amphetamine-like sympathomimetic drugs, including PPA. Just two- to three times the therapeutic dose of ephedrine or PPA may likely be a contributing cause of significant hypertension in some people. [Pentel 1984] This narrow window may likely account for the relatively high incidence of adverse effects after both accidental and intentional overdose of ephedra and the adverse events reported after ingestion of recommended doses. Although serious adverse reactions are not frequently reported, serious harm may result in otherwise healthy individuals even after exposure to relatively small doses of ephedrine. [Haller and Benowitz 2000; Samenuk 2002; *See also* Section IV(A) below] Given the substantial variability among individuals in their blood pressure responses to PPA and ephedrine containing supplements, these drugs' low therapeutic window may be especially significant.

C. Mechanisms of Amphetamine-like Sympathomimetics, Including Ephedrine

37. The mechanisms in a susceptible individual may be either idiosyncratic or multifactorial. Vasoconstriction within the coronary vascular bed and, in some cases, vasospasm, are believed to be the mechanisms of myocarditis and myocardial infarction. Ephedrine may predispose patients to both hemorrhagic and ischemic stroke. The likely mechanisms involve hypertension and vasoconstriction, and possibly other types of cerebral vasculopathy (likely results from the hypertensive action of ephedrine), which may be short-lived. It may also play a role in cerebral vasculitis, which has been described in association with a variety of sympathomimetic drugs. [Green 1990] One mechanism of ischemic/thrombotic stroke is presumably related to vasoconstriction of large, medium or smaller cerebral arteries or arterioles, which may lead to local thrombosis as a result of stasis and sympathomimetic-induced platelet activation. [Haller and Benowitz 2000]

1. Ephedrine, like other amphetamine-like drugs may likely be a contributing cause of vasoconstriction or beading.

38. Arterial vasoconstriction, either transient or chronic, has frequently been suspected as a mechanism for ischemic stroke following drug use. Cocaine has been the most clinically studied of the sympathomimetic class of drugs. Many studies have demonstrated vasoconstriction arteriographically, in the cerebral, coronary, and peripheral vasculature with use of sympathomimetics. [Yu 1983; Stoessel 1985; Kase 1987; Maertens 1987; Le Coz 1988; Rothrock 1988; Forman 1985; Greene 1990; Barinagarramenteria 1990; Ryu 1995] Inflammation in the vessel wall (vasculitis or arteritis) has been suggested by a number of studies. [Citron 1970; Margolis 1971] "Beading" on angiography can be suggestive of an inflammatory vascular process, but it is still non-specific and requires pathological confirmation (biopsy).

39. Arteritis or "beading" is also described in the published medical literature with ephedrine use. [Wooten 1983; Yin 1990; Mourand 1999] In the textbook, *Uncommon Causes of Stroke*, published in 2001, Singhal *et al.* list ephedrine and other sympathomimetics in Table 15.1 as associated with reversible cerebral vasoconstriction.

2. Ephedrine, like other amphetamine-like sympathomimetics, may likely be a contributing cause of deep lacunar infarcts.

40. Small vessel disease may lead to subcortical, small, deep lacunar infarts in the brain. These types of strokes have been reported with cocaine and other sympathomimetics [Levine *Neurology* 1987, Levine *Neurology* 1991, Green, *Stroke* 1990; Montalban 1989; Bernstein, Diskant 1982; Johnson 1983, Edwards 1987, Golbe *Neurology* 1986].

41. When cerebral angiography has been performed to visualize the cerebral vessels, it is usually normal, although reports have demonstrated middle cerebral artery (MCA) stenosis, and distal MCA or bilateral anterior cerebral artery occlusions. Possible explanations for these small deep infarcts in individual cases include: vasospasm of small penetrating arteries, vasospasm of main-stem cerebral arteries with ischemia in the distribution of the penetrating arteries, vasospasm superimposed on macroatheroma or microatheroma (as some patients had

other stroke risk factors such as hypertension and cigarette smoking), embolism, or some other mechanism yet to be further defined.

42. There appears to be not just a selective cerebrovascular effect by ephedrine. Drug-induced structural heart disease may lead to stroke in some people through cardiogenic embolism. Ephedrine has been linked in the published peer-reviewed medical literature to myocardial infarction [Perrotta, 1996; Cockings 1997; Theoharides 1997; Traub 2001], which then may be a contributing cause of cardioembolic stroke. [Haller & Benowitz 2000] This is especially true if the MI involves the anterior/lateral wall and septum. Symathomimetics may be a contributing cause of myocardial wall injury, as well as coronary intimal hyperplasia (as seen with cocaine), and cardiomyopathy. The cardiomyopathy may be reversible or chronic. [Fenoglio and Silver, Ch. 32, 1991; Zaacks 1999; Samenuk 2002; Naik 2004] Sympathomimetic drugs have also been associated in the published medical literature with vasospasm of the coronary vessels. [Hirabayashi 1996.]

IV. PUBLISHED PEER-REVIEWED LITERATURE PROVIDE EVIDENCE THAT SYMPATHOMIMETICS, INCLUDING EPHEDRINE AND EPHEDRA DIETARY SUPPLEMENTS, MAY LIKELY BE A CONTRIBUTING CAUSE OF STROKE.

43. Over the past 40 years, a large number of case reports in medical journals, letters to the editor within the peer-reviewed medical literature, case series, autopsies, and epidemiological studies have reported stroke and cerebrovascular disease following ingestion of both illicit and widely available (including over-the-counter) sympathomimetic drugs, including ephedrine. Both ischemic and hemorrhagic strokes have been reported, occurring from early childhood into the elderly, and in both males and females. Ischemic and hemorrhagic strokes have been reported specifically with ephedrine/ephedra use, in addition to the reports concerning other similar acting drugs.

44. All subtypes of stroke have been reported, including temporary and permanent neurological deficits and disabilities from blood vessels supplying blood to the eye, brain, brain stem, and cerebellum.

A. Case Reports and Case Series Describe a Likely Association Between Ephedrine/Ephedra Containing Substances and Strokes

45. Case reports are important clinical evidence of causal association of a drug to a particular disease, especially where such reports are consistent with similar findings in a growing body of case reports, animal and clinical studies, and – if available – epidemiologic data. Case reports are often the only source of information available to describe in detail the effects of toxic agents. Case reports generally provide a complete description of the patient's symptoms, as well as details regarding exposure to the toxin, the temporal relationship to onset of symptoms, and the plausibility of exposure and disease. Published case reports are also both relevant and important to physicians in a clinical setting because they provide valuable information necessary to guide in the diagnosis and treatment of life-threatening conditions. [Vanderbroucke 2001]

46. Published reports as far back as 1983 have described a likely association between ephedrine and stroke. [Wooten 1983] Wooten and colleagues reported a case of subarachnoid hemorrhage and vasculitis in a 20-year old man following ephedrine use.

47. In 1990, Dr. Pu-An Yin reported a case of a 68-year old man who suffered a hemorrhagic stroke and vasculitis shortly after taking an over-the-counter asthma remedy containing ephedrine. The author found that this patient's vasculitis was similar to that seen with other sympathomimetics. Dr. Yin concluded, "Our case underscores that a patient with intracerebral hematoma and no obvious etiology should be evaluated for drug-induced vasculitis." [Yin 1990]

48. In 1993, Bruno and colleagues reported three cases of ephedrine-related stroke. Two of the patients suffered hemorrhagic strokes, and one had an ischemic stroke. The authors stated, "These observations, and the reported link between other sympathomimetic drugs and stroke, suggest that ephedrine alone also may predispose to stroke." The authors also urged restrictions on the availability of ephedrine. [Bruno 1993]

49. In 1999, Mourand and colleagues described a case of multiple infarcts and "beading" in a 44-year old woman who had been administered ephedrine during spinal anesthesia for varicose vein surgery. The authors noted the similarity of this patient's stroke and the beading appearance to other cases of stroke reported in the literature as possibly or probably induced by amphetamine, PPA, pseudoephedrine or ephedrine. [Mourand 1999]

50. As the popularity of "herbal" ephedrine containing dietary supplements rose in the late 1990s, so did the number of reports in the peer-reviewed published literature. In 2000, Vahedi and colleagues reported a case of ischemic stroke in a young athlete after ingesting an ephedra dietary supplement in combination with creatine. [Vahedi 2000]

51. In 2000, duBoisqueheneuc and colleagues published a report involving a 33-year old female patient who suffered an ischemic stroke after ingesting "Ripped Fuel", an ephedra dietary supplement. The authors called for regulation and public education of the dangers of herbal supplements. [duBoisqueheneuc 2000]

52. In 2002, Kaberi-Oterod and colleagues described an ephedra-related ischemic stroke in a 33-year old man with no apparent risk factors. [Kaberi-Oterod 2002]

53. In 2003, Foxford and colleagues reported a case of vasospasm-induced ischemic stroke associated with ephedra in a young, healthy male athlete. Echocardiogram tests ruled out embolism as a source. Angiography revealed narrowing of the right middle cerebral and right internal carotid arteries. [Foxford 2003]

54. In 2004, Chen and colleagues published five cases of ephedra related ischemic strokes and vasculitis over a two-year period. The authors noted a likely association between sympathomimetic drugs and strokes [Chen 2004].

B. <u>Analysis of Adverse Events Received by FDA Provides Additional Evidence that Ephedra May Likely Cause Stroke.</u>

55. From 1995 to 1997, 926 cases of possible ephedrine toxicity were reported to the FDA. These were reviewed by Samenuk et al. in 2002. In 37 patients (23 women and 14 men, mean age 43 years +/- 13 years), ephedrine was temporally related to stroke (16 cases, 3

fatal), myocardial infarction (10 cases), or sudden death (11 cases). In 36 of the 37 cases, use of ephedrine containing products was reported to be within the manufacturers' dosing guidelines.

56. Of the stroke cases, 4 were men and 12 were women. Average age was 44 years ± 13 years (range was 24-69 years). Of these 16 patients, 12 (75%) had an ischemic stroke and four (25%) had a hemorrhagic stroke.

57. In 2000, Haller and Benowitz reviewed 140 adverse events associated with ephedrine that were submitted to the FDA between June 1, 1997 and March 31, 1999. Four strokes and one TIA were suspected of being related to ephedrine; six strokes were possibly related. Duration of use in the 11 cases definitively or probably related to ephedrine was from one day to one year, with five patients having a duration of use from one to three weeks before their adverse event.

58. Haller and Benowitz outlined several characteristics of individuals that would help explain substantial differences in individual susceptibility, including kidney disease (which can reduce the rate of elimination of ephedrine alkaloids), alkaline urine (reducing the rate of elimination), pre-existing coronary or cerebrovascular disease, underlying hypertension, autonomic insufficiency (augmenting pressor response to stimulants by 10- to 100-fold), hyperthyroidism (acting in concert with ephedrines), psychiatric disease, history of a seizure disorder, and diabetes.

59. It is clear that adverse reactions to ephedrine are uncommon, but that ephedra may be a contributing cause of potentially serious harm in some people. As Haller and Benowitz state:

> "The quantity of ephedrine in dietary supplements, as reported on package labels, is typically about 20 mg per serving, and the usual dose frequency is two to three times per day. These products may contain larger or smaller amounts of ephedra alkaloids than are listed on the product label. For example, 11 of 20 supplements tested by Gurley et al. either failed to list the alkaloid content on the label or had more than a 20 percent difference between the amount listed on the label and the actual amount. Often, the dose of ephedrine that was associated with an adverse event was less than a typical dose of ephedrine used for bronchodilation (25 to 50 mg). Experimental studies show that ephedrine has only moderate

> effects on heart rate and blood pressure at these doses. The discrepancy between such data and the precipitation of stroke and other serious adverse events reported with the use of dietary supplements containing ephedra alkaloids may be due to individual susceptibility, the additive stimulant effects of caffeine, the variability in the contents of pharmacologically active chemicals in the products, or preexisting medical conditions."

60. The RAND study also found additional cases of stroke and other adverse cardiovascular events found within the Metabolife database, which was provided to the FDA pursuant to subpoena.

C. Epidemiological Studies and Ephedra

61. There are obvious limitations with undertaking an epidemiology study to determine the frequency of a serious, life threatening adverse reaction. In the case of ephedra and PPA, it would be unethical to conduct a Class I prospective double-blind study to investigate the risk of stroke as the end-point, due to known safety concerns of these drugs and the fact that the FDA has banned their sale in the United States and elsewhere. Therefore, there is very little likelihood that there will ever be any Class I evidence to prove a definitive causal relationship between ephedra and stroke.

62. The only epidemiology study that was conducted to look at ephedra and the risk of stroke was a subanalysis of the Hemorrhagic Stroke Project ("HSP"). The HSP was a case-control study of 702 subjects (i.e., a Class II study). It was designed to quantify the association between PPA and the risk of hemorrhagic stroke. The results showed an increased risk of hemorrhagic stroke in women and in any "first-time" user of PPA regardless of gender. As part of the standardized history of patients taken within the study protocol, the investigators also found 7 subjects who had been exposed to ephedra. The researchers conducted a statistical analysis to determine the risk of stroke in the subgroup of ephedra subjects. The study concluded that there was no increased risk of hemorrhagic stroke at daily doses under 32 mg/day (OR 0.13; 95% CI 0.01 to 1.54). However, at higher doses, there wasa 3.5-fold increased risk in the group studied (OR 3.59; 95% CI 0.70 to 18.35), which may likely reflect an increased risk among ephedra users in general, though the data was underpowered and did not meet the

conventional standard of statistical significance. [Morgenstern et al. 2003] Notably, the typical recommended daily dose of ephedrine for many ephedra supplements far exceeds 32 mg/day.

63. The HSP represents additional data from secondary analyses on ephedra and stroke that is consistent with the body of literature on the topic. Because of possible bias in questioning, the number of exposed cases may well have been underreported, since subjects may not have known that dietary supplements fit into the category of "all medications and diet aids" (product identification). Excluded from eligibility were cases involving serious injury or death, which may also have contributed to underreporting. In addition, the HSP did not include ischemic strokes, which account for a higher percentage of reported ephedra-induced strokes than PPA (approximately 75% ischemic vs. 25% hemorrhagic). Furthermore, the small numbers of exposed cases casts doubt on the statistical strength of the study to detect a relatively rare but serious injury such as stroke.

64. I rely on the inferences drawn from the HSP data, combined with the other multiple and consistent lines of evidence described in this report, that ephedra may likely be a contributing cause of hemorrhagic strokes in some people. It is possible that well-designed controlled clinical studies may be conducted in the future to determine whether ephedra causes a statistically significant increase in hemorrhagic strokes in humans. If and when such studies are done, they may disprove my opinion.

65. Shekelle et al. (*JAMA* 2003) synthesized the data on ephedra and efficacy for both weight loss and athletic performance and reviewed adverse events. They concluded that there is likely a two- to three-fold increase in adverse events, including those affecting autonomic nervous system, compared to placebo.

V. MEDICAL TEXTBOOKS AND OTHER LEARNED TREATISES PROVIDE ADDITIONAL SUPPORT THAT EPHEDRINE-CONTAINING DIETARY SUPPLEMENTS MAY LIKELY BE A CONTRIBUTING CAUSE OF STROKES IN SOME PEOPLE.

66. In addition to case reports and biological plausibility, medical textbooks, treatment guidelines, and consensus statements by medical organizations generally express the

view that there may likely be a relationship between ephedrine-containing drugs and all stroke subtypes. For example, Adams, Hachinski and Norris list, Stroke as a potential complication of medications that have vasoconstrictive properties. Among the medications that have been implicated are PPA and ephedrine. [Adams, Ch. 9, 2001.]

67. According to the most recent edition of a major Stroke textbook edited by J.P. Mohr and colleagues, both ephedrine and dietary supplements containing ephedra alkaloids may be associated with both hemorrhagic and ischemic stroke. [Brust Ch. 35, 2004]; *See also* the medical textbook *Primer on Cerebrovascular Disease*. [Sloan Ch. 113, 1997.]

68. The renowned pharmacology textbook by Goodman & Gilman, *The Pharmacological Basis of Therapeutics* states:

> "Concerns have been raised about the safety of ephedrine. Usual or higher than recommended doses may cause important adverse effects in susceptible individuals and may be especially of concern in patients with underlying cardiovascular disease that might be unrecognized. Of potentially greater cause for concern, large amounts of herbal preparations containing ephedrine (ma huang, *Ephedra*) are utilized around the world. There can be considerable variability in the content of ephedrine in these preparations, which may lead to inadvertent consumption of higher than usual doses of ephedrine and its isomers."
>
> [Hoffman and Lefkowitz, Ch. 10, 2001 at 238.]

VI. DIFFERENTIAL DIAGNOSIS IS AN ACCEPTED MEDICAL METHODOLOGY FOR DETERMINING THAT EPHEDRINE MAY LIKELY BE A CONTRIBUTING CAUSE OF STROKES

69. Differential diagnosis is a well-established medical methodology. It is routinely relied upon by physicians in a clinical setting to diagnose and treat patients with life-threatening conditions. Differential diagnosis also incorporates principles set forth by Karch and Lasagna and is relied upon by physicians to guide their analysis in diagnosing drug-related side effects. In the literature cited above in Section IV, clinical physicians have diagnosed ephedrine and ephedra as a likely contributing cause of patients' acute neurological symptoms after a thorough and careful evaluation using standard diagnostic techniques. They published their findings in the peer-reviewed literature, with the recommendation that physicians put ephedrine

and ephedrine-containing dietary supplements on their list of possible causes and etiological factors to consider, particularly where no other likely cause is found.

A. Clinical Presentation of Stroke and Stroke Subtypes That May Likely Be Related to the Use of Sympathomimetics, including Ephedrine

70. Typically (in about 85% to 90% of cases), the age range for strokes that may likely be related to sympathomimetic use occurs in the third or fourth decade of life, with the range of ages reported from neonate/perinate to 63 years of age. The average age was 41 years in the Baltimore-Washington regional study by Sloan et al. [*Neurology* 1991] For illicit drugs, men were predominantly involved. For PPA, women were predominantly affected. There does not appear to be a racial predilection apart from the bias of drug use and abuse in selected populations.

71. Symptoms may occur in the background of chronic use/abuse, overdose, "binge" use, re-exposure after a prolonged abstinence, or even first exposure to the offending agents. Symptoms may frequently occur during or within minutes to several hours (usually within 48 to 72 hours) after administration of the drug. Routes of intake have included intravenous, intranasal, inhalation, oral, intramuscular, subcutaneous, or inadvertent intra-arterial.

72. There may be a strong temporal association between drug use and stroke. This is one of the Karch & Lasagna postulates for causation (defining and proving a causal/etiologic relationship).

B. An Analysis of the Likely Mechanisms of Hemorrhagic Stroke in Relationship to Sympathomimetics, and specifically Ephedrine

73. Because stroke without pre-existing medical conditions (i.e., stroke risk factors such as hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, and heart disease) is distinctly unusual in people under the age of 50, there needs to be a high clinical index of suspicion for drug use or abuse when a cerebrovascular accident occurs. [Sloan 1997; Adams 2001; Hoffman & Lefkowitz, Ch. 10; Gurley 2000; Yin 1990] Ideally, a toxicology

screen for both licit and illicit substances is a recommended part of the diagnostic evaluation of such patients. Neurodiagnostic studies to establish etiology include brain imaging should preferably include an MRI, and at least a head CT scan to determine type, location, and size of the cerebrovascular event. Cardiac sources of embolism are evaluation by cardiac history, auscultation, 12-lead EKG and rhythm strip, cardiac enzyme levels, and echocardiography.

74. Cerebral angiography, which generally has a high yield for detecting abnormalities in young stroke patients if performed shortly after the event, may demonstrate extracranial or intracranial large vessel lesions (stenosis, occlusion, beading, aneurysm, AVM).

VII. CONCLUSION

75. Sympathomimetic agents may likely be a contributing cause of both hemorrhagic and ischemic strokes in some people. Examples of these sympathomimetic drugs are cocaine, amphetamine, and PPA. Ephedrine has similar pharmacologic characteristics and side effects to other amphetamine-like sympathomimetics. All of these drugs are potent vasoconstrictors and may likely be a contributing cause transient increases in blood pressure in some people. There is a growing body of published literature, textbooks, and learned treatises in the fields of pharmacology, toxicology, and neurology that ephedrine-containing substances may be a contributing cause both ischemic and hemorrhagic stroke in some people, where there is a close temporal relationship between ingestion and onset of symptoms, and where other probable etiologies are excluded. The scientific knowledge regarding the ability of ephedra to be a likely contributing cause strokes in some people is consistent with what we already know about the pharmacological properties and adverse event profiles of similar amphetamine-like sympathomimetics. These combined and consistent lines of evidence support a likely, although not scientifically proven, causal relationship between ephedrine-containing dietary supplements and stroke. Large, well-designed controlled clinical studies, if and when they are conducted, would provide definitive scientific evidence that may disprove a causal relationship between ephedra and stroke.

76. For all of the reasons set forth above, it is my opinion that ephedra may likely be a contributing cause of ischemic and hemorrhagic strokes in some people.

77. I have given courtroom testimony as an expert approximately 7 times in the past 5 years. I have also given deposition testimony at the rate of approximately 5-7 depositions per year for the past 5 years.

78. My hourly rate for legal consultation is $500 per hour. I charge $1,000 per hour for testifying in deposition.

Dated: February 27th, 2006.

Steven R. Levine, M.D.

Submitted by the PCC this 28th day of February, 2006.

Respectfully submitted,

By: _____

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CERTIFICATE OF SERVICE

I hereby certify that a true copy of the foregoing was served electronically via e-mail to the DCC via defense liaison counsel, Peter Neger at peter.neger@bingham.com; and to James Niss, Special Master at james.niss@verizon.net on the 28th day of February, 2006.

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